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13. ABSTRACT ***(Maximum 200 Words)***

The objective of this project is the development of new chemotherapeutic agents for the treatment of hormone-responsive breast cancer using a solid phase approach to synthesize new agents having features common to both steroids and antiestrogens. During the past year we have functionalized the carboxy resin with both the E-and Z-tributylstannylvinyl estradiol. We have prepared and characterized the initial series of iodophenoxyalkylamines that will be coupled to the resin-bound steroid. The biological assays have been established and validated using series of previously prepared compounds. Molecular modeling and NMR spectrometric methods for conformational analyses and for data analysis have been developed. The next years specific aims involve the synthesis and evaluation of the initial series of target compounds.

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R J Thomson 7 Dec. 2001

P.I.

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5. Introduction

The overall objective of this project is the development of new chemotherapeutic agents for the treatment or prevention of hormone-responsive breast cancer. Based upon our precious synthetic work and molecular modeling studies, we undertook the preparation of a series of 17α-(substituted phenylvinyl) estradiols using a solid-phase synthesis approach. The key feature of these compounds is the incorporation onto the phenylvinyl group of the dialkylaminoalkoxy side chain found in the potent anti-estrogens tamoxifen and raloxifene. This would be accompanied by the development of the appropriate biological assays to determine bioactivity and NMR evaluations to determine the molecular bsis for the observed effects. In this report we describe the preliminary aspects of this work and the advances that we have made in these areas.

6. Body

The research proposal described 5 Tasks as part of the Statement of Work. These included: 1. Initial target compound design. 2. Chemical synthesis of target compounds in initail directed library. 3. Measurement of biological properties-affinity and efficacy.4. Assessment of structure-activity relationships. 5. Chemical synthesis of target compounds in second generation libraries. Work has been undertaken on the first three tasks and will be described in the report.

Task 1. Initial target compound design (Pre-award).

Prior to the initaition of the award, we evaluated the SAR for the tamoxifen and raloxifene anti-estrogens and selected the structural variations for the dialkylaminoalkoxy side chains. Based upon our analysis of the crystal structures for liganded ER-LBDs, we chose to prepare the dimethylamino-, diethylamino-, pyrrolidino- and piperidino- tertiary amines with ethoxy, propoxy- and butoxy- side chains situated at the ortho-, meta- or para- positions of the phenyl ring. The starting materials were purchased from commercial sources. The methods for the biological assays were identified as well.

Task 2, Chemical synthesis of target compounds in initial directed library (Months 1-18).

During this period we have focused on two aspects. The first is the preparation of the functionalized resin that will be used in the combinatorial chemistry. The second is

the preparation of the iodophenoxy precursors for the penultimate coupling step. For the first part, we have prepared on large scale the E- and Z-17a-tributylstannyl vinyl estradiol isomers. While the E-isomer predominated (7.5g vs. 2.0 g), there was sufficient quantities of both to perform the coupling to the carboxy resin (polystyrene backbone). We used carbonyl diimidazole as the coupling reagent. For the second part, we used the commercially available ortho-, meta- and para-iodophenols as starting materials. These could be coupled directly with the commercially available N-hydroxyethyl amines using the Mitsunobu reaction. Preparation of the corresponding N-hydroxypropyl- and N-hydroxybutyl- derivatives was accomplished in two steps. We employed the Mitsunobu reaction to couple the phenol to the w-halopropan(butan)ol followed by amination with the desired secondary amine. The final compounds were characterized by NMR and MS.

The project is now ready to undertake the solid-phase coupling of the two components using the Stille reaction conditions that we have used in other studies.

Task 3. Measurement of biological properties-affinity and efficacy (Months 1-36).

We have established the biological assay systems for evaluating the compounds and have begun to determine their properties. Our initial results examined the effect of stereochemistry (E-vs Z-) and position (o-/m-/p-) on receptor binding for the hydroxyphenyl vinyl estradiols and for the para-methoxyphenyl vinyl estradiols. In this series, the hydroxy and methoxy substituents are well tolerated. Although the binding

(RBA values) are less than estradiol, except for the E-m-hydroxyphenyl compound which is comparable to estradiol itself, they are equal to or better than the unsubstituted phenyl vinyl estradiol. Only the value for the Z-m-isomer is unavailable at this time. The uterotrophic growth assay will be done in the near future to determine the efficacy of the compounds and establish a baseline against which the dialkylaminoalkoxyphenyl products can be compared.

One key aspect in this portion of the project that was determined in one of our other programs was the need to do the in vivo assays with a single lot of animals. The lot to lot variation was too great to permit a reliable comparison of results for compounds in a series performed at different times. Therefore, we have to wait until we have all six isomers of a series (E-/Z-; o-/m-/p-) before conducting an assay.

Task 4. Assessment of structure-biological activity relationships (Months 6-36).

We have utilized both NMR (H-1;C-13) and molecular modeling to examine the conformation of the substituted phenyl vinyl estradiols. In general, the molecular modeling provides several reasonable low energy conformers for the compounds. Two of these conformers are observed in solution using NMR. However, the energy barrier between the two (and sometimes three) low energy conformers is low and it appears that small energy contributions from the receptor protein could easily induce a change to give a conformation not favored in solution or necessarily predicted by computational methods. We have undertaken the evaluation of the ER-LBD based on the several

published structures. This evaluation includes molecular dynamics with and without bound ligand. Since several of the initial compounds that we have evaluated in other studies are estrogen receptor agonists, our first studies utilized the agonist form of the receptor. As we get more information about our new ligands, we can investigate their docking modes with the antagonist form of the receptor. To date, our studies suggest that there is significant interaction between the substituted phenyl vinyl group and the amino acid sidechains present in the helix-11/12 region but definite sites cannot be identified.

7. Key Research Accomplishments.

- Prepared functionalized resin with both E- and Z-triabutylstannylvinyl estradiol
- Prepared many of the dialkylaminoalkoxyphenyl iodide coupling reagents
- Developed appropriate NMR and molecular modeling methods using structurally similar estradiol derivatives
- Developed biological assays and validated methods using structurally similar estradiol derivatives
- Initiated SAR studies using data from parallel series of compounds

8. Reportable Outcomes.

a. Manuscripts, abstracts, presentations.

1. Sebag, A.B., Hanson, R.N., Forsyth, D.A., and Lee, C.-Y., Conformational studies of novel estrogen receptor ligands by 1D and 2D NMR spectroscopy and computational methods. Org. Magn. Res. (accepted pending minor revisions).

2. Hanson, R.N., Design, synthesis and evaluation of novel steroidal antiestrogens for the treatment of hormone responsive breast cancer. Invited presentation at The Philip S. Portoghese Symposium in Medicinal Chemistry, August 23-24, 2001, Minneapolis, Minnesota.

a. Degrees obtained supported by the award.

None.

9. Conclusions.

At this point we have achieved several of the intermediate objectives of the project. We have prepared the E- and Z-tributylstannylvinyl estradiols and coupled them to the carboxy resin. We have prepared a number of the dialkylaminoalkoxyphenyl iodides that will we used to react with the functionalized resin. Using our Stille coupling procedure we have prepared sample substituted phenylvinyl estradiol derivatives on the resin and submitted them to validate our biological assays. We have established the assay for receptor affinity using the ER-LBD overexpressed in the BL-21 cell line. We are

working on the MCF-7 cell proliferation assay to generate the reproducibility necessary for this project. We have established the immature rat uterotrophic growth assay and tested it using a set of estradiol derivatives made previously. These results suggest significant differences in potency exist between E- and Z-, ortho-, meta- and para-isomers. Progress made to date in all areas of the project indicate that goals for the next year are achievable.

10. References:

None.

11. Appendix:

The appendix material is comprised of copies of one manuscript accepted for publication in Organic Magnetic Resonance, pending final revisions, and the brochure for The Philip S. Portoghese Symposium in Medicinal Chemistry.

Conformational Studies of Novel Estrogen Receptor Ligands by 1D and 2D NMR Spectroscopy and Computational Methods

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Abstract: The solution conformations of the novel estrogen receptor ligands, (17α, 20E)-(p-α, α, α-trifluoromethylphenyl)vinyl estradiol (**1**) and (17α, 20E)-(o-α, α, α-trifluoromethylphenyl)vinyl estradiol (**2**) were investigated in 2D and 1D NOESY studies and by comparison of ^{13}C NMR chemical shifts with theoretical shieldings. The ^{1}H and ^{13}C assignments of **1** and **2** were determined by DEPT, COSY, and HMQC experiments. The conformations of the 17α-phenylvinyl substituents of **1** and **2** are of interest because of their differing receptor binding affinities and effects in MCF-7 cell proliferation assays. A statistical method of evaluating contributing conformers of **1** and **2** from predicted ^{13}C shifts of possible structures correlated quite well with conformational conclusions derived from the NOE data. The 17α substituents of **1** and **2** apparently have a similar conformational preference in solution, suggesting that **1** and **2** could occupy a similar receptor volume.

Introduction

As part of our efforts to develop more effective therapeutic agents for the treatment of breast cancer, we undertook the designing of (17α, 20E)-(X-phenyl)vinyl estradiol compounds that can potently and selectively block the interaction of estradiol with its target receptor to impart the desired biological effect. In MCF-7 cell proliferation assay studies, we observed that (17α, 20E)-(p-α, α, α-trifluoromethylphenyl)vinyl estradiol (**1**) antagonizes estradiol stimulation and is a very weak agonist with a relative binding affinity (RBA) of 7, compared to the native ligand estradiol at 100.[1] In contrast, under the same assay conditions, (17α, 20E)-(o-α, α, α-trifluoromethylphenyl)vinyl estradiol (**2**) was a full agonist with an RBA of 71. We examine here whether *ortho vs. para* placement of the substituent in these *E*-isomers could produce a difference between the preferred conformations of **1** and **2** that could account for their distinguishable biological responses and varying binding affinity. In particular, if the conformational preferences differ and that difference were to be preserved upon binding to the receptor, it could affect the conformational mobility of the key helix-12 of the ligand binding domain (LBD) of the estrogen receptor (ER).[2]

Recently we showed that the placement of a substituent in the *ortho* or *para* position in some *Z*-isomers, i.e., (17α, 20Z)-phenylvinyl estradiols did affect the conformational equilibrium of the 17α side chain.[3] In that study, (17α, 20Z)-(p-methoxyphenyl)vinyl estradiol and (17α, 20Z)-(o-α,α,α-trifluoromethylphenyl)vinyl estradiol were found to exist in similar conformational equilibria which suggested they would likely occupy a similar receptor volume. These results were consistent with their similar RBA values of 20 and 23. In contrast, (17α, 20Z)-(o-hydroxymethylphenyl)vinyl

estradiol, which had an RBA of 140, was found to exist in a different conformational equilibrium in terms of the distribution of structures varying in the angles of rotation about the bonds to the vinyl group. These results suggested that, in addition to position and electronic effects of the substituent, the preferred conformations of the 17α substituent of Z-compounds might account for some variation of the RBA values.

In this report, we present a conformational study of the 20E-isomers, **1** and **2,** using NMR and computational methods, to determine whether differences in the preferred conformation of **1** and **2** might also account for their distinguishable biological responses and binding affinities.

The key conformational feature to establish for **1** and **2** is the orientation of the 17α substituent relative to the steroid skeleton. In this study, we use molecular mechanics calculations to generate a set of possible conformations. Two types of NMR data are used in conjunction with the predicted conformations to evaluate which conformations are populated in solution. One approach is to use ^{13}C chemical shifts in a comparison with shifts predicted for each of the geometries generated from the molecular mechanics calculations. The predicted ^{13}C shifts come from empirically scaled GIAO (gauge including atomic orbitals) shielding calculations.[4] The other approach is to compare ^{1}H-^{1}H nuclear Overhauser effects established in one- and two-dimensional experiments, 1D and 2D NOESY, with predicted interatomic distances.

Experimental

The syntheses and biological data of compounds **1** and **2** have been described elsewhere.[5] ^{1}H NMR data were recorded at 25 °C for 5-8 mg samples dissolved in acetone-d_6 in 5 mm NMR tubes using a Varian Unity 500 MHz NMR spectrometer

equipped with a 5 mm Varian inverse probe. DEPT and ^{13}C experiments were obtained on a Varian Mercury instrument at 75 MHz.

^{1}H spectra were obtained with a spectral width (SW) of 8 kHz, a 67° pulse flip angle, a 1.7 s acquisition time (AT), a 2 s relaxation delay (RD) and digitized with 32768 points giving a digital resolution (DR) of 0.488 HZ per point. Chemical shifts were referenced to the residual ^{1}H signal of acetone-d_6.

^{1}H-decoupled ^{13}C spectra were recorded with a 18856 Hz SW, a 60° pulse flip angle, a 2 s RD and digitized into 65536 points to give a digital resolution of 0.575 Hz per point.

HMQC[6] experiments for single bond ^{1}H, ^{13}C chemical shift correlation spectra utilized the BIRD sequence to suppress unwanted signals and GARP[7] ^{13}C decoupling. Two sets of 256 time increments were obtained in the phase-sensitive mode with 32 transients obtained per time increment and a 2 s RD. The final matrix was processed with Gaussian functions.

COSY45[8] experiments were performed with 8 scans for each of 200 increments in F_1, 2048 data points in F_2 and a relaxation delay of 2.0 s. The final matrix was symmetrized and processed with sine-bell exponential multiplication.

NOESY[9] experiments were performed with 32 scans for each of 256 F_1 increments, 2048 data points in F_2, with a relaxation delay of 2.0 s and a mixing time of 0.500 s. The final matrix was not symmetrized, but was processed with Gaussian weighing functions.

1D NOESY[10] spectra were obtained using a spectral width of 5000 Hz and 20500 points giving a digital resolution of 0.490 Hz per point, a mixing time of 0.500 s, a RD of

2.0 s, and a AT of 1.7 s. A Gaussian shaped pulse was used for selective irradiation.

RESULTS AND DISCUSSION

^{1}H and ^{13}C Assignments

The ^{1}H NMR spectra of **1** and **2** in acetone-d_6 (Figures 1(a) and 2(a)) exhibit very little chemical shift dispersion in the low frequency spectral regions (1.2-2.5 ppm), precluding straightforward ^{1}H assignment even at 500 MHz. However, ^{1}H signals were assigned via application of HMQC and COSY techniques. The first step was to make ^{13}C shift assignments, based on our earlier studies of several 17α-substituted estradiols,[3] DEPT experiments, and theoretical shielding calculations (see below). Then, geminal proton resonances were identified and all proton signals were correlated with directly attached carbons via an HMQC experiment. COSY experiments confirmed the initial assignments made by the HMQC experiment but did not, of course, distinguish between α and β hydrogens in a given methylene group. This distinction was readily achieved by 1D NOESY experiments (Figure 1(b) and 2(b)). Using a Gaussian pulse, selective irradiation of the protons of the methyl group enhances protons on the β face of the C and D rings, viz., 11β, 12β, 15β, 16β, and H8. Table 1 lists the complete assignments of the ^{1}H and ^{13}C signals of **1** and **2**.

Theoretical Carbon Chemical Shifts and Conformational Determination

The predicted low energy conformers of **1** and **2** (Figures 3 and 4) were generated using the MM3[11] force field through conformational searching by a previously described method.[3] The key dihedral angles are listed in Table 2 for the lowest energy conformers,

1a-1c and **2a-2h**, with energies within 1.6 kcal of the lowest energy conformers for **1** and **2**, respectively.

As the MM3 calculations show, significant changes in the 17α side chain conformation result in only minor energy differences. Most of the low energy conformers are within 1 kcal of the lowest energy conformer, making any conformational determination based purely on MM3 energy predictions unreliable. In MMX[12] and MM3 force fields, driving the dihedral angle C21-C20-C17-C13 shows a very shallow energy surface from 85° to 165. In this region, discrete changes in the orientation of the phenyl to the vinyl group yielded numerous minima using either MM3 or MMX. Conformers **1a** and **1c** were kept as minima since they represent the upper and lower dihedral range of this shallow surface.

Conclusions regarding the preferred 17α side chain conformation of **1** and **2** were approached by applying a statistical method of determining contributing conformers from predicted ^{13}C chemical shifts, δ_{pred}, of MM3 determined conformers.[3,13] The δ_{pred} were calculated for each MM3-predicted conformer by empirically scaling GIAO-calculated absolute shieldings, σ, obtained at the B3LYP/3-21G level with heteroatoms augmented at the 6-31+G* level.[4] All shielding calculations were carried out with the Gaussian98 program.[14] Tables 3 and 4 list the δ_{pred} of each MM3 conformer and the assigned experimental ^{13}C chemical shifts, δ_{exp}.

In this statistical method, the predicted ^{13}C shifts of the C and D rings of all MM3 conformers of **1** and **2** were in each separate case treated as independent variables in a multiple independent variable regression analysis of the corresponding experimental data.[15]

The predicted ^{13}C shifts of the A and B rings of all reasonable conformers of **1** and **2** were not used in this statistical analysis since all remain the same within 0.5 ppm regardless of the conformer. In contrast, while the shift differences are still relatively small,[4] most carbons in the C and D rings of **1** and **2** display larger than 1 ppm shift differences depending on the geometry. The regression analysis yielded fractional populations as the fitting parameters. All standard errors and confidence levels of the regression analysis were estimated using the Bootstrapping method.[16]

The results and corresponding estimates of uncertainties (standard errors) are listed in Table 5. Both **1** and **2** were found to have a major conformer, **1b**, 72 ± 32%, and **2e,** 65 ± 33%. Minor conformers are also indicated for each: **1a**, 13 ± 29%, and **1c**, 15 ± 28%; and **2c**, 33 ± 18%, and **2h**, 2 ± 22%. It is important to note that the large corresponding standard errors make conclusions on the presence of minor conformers unreliable.

The success of this statistical approach for deducing percentage populations of participating conformations in fast exchange depends upon several conditions. Obviously, the molecular mechanics calculations must correctly identify all the possible contributing conformations and represent their conformations appropriately. The chemical shift calculations must also be reasonably accurate; confidence in this regard is engendered by the close match of predicted chemical shifts to experimental shifts at the positions that do not have conformationally dependent shifts. Finally, there must be substantial differences in chemical shifts among the possible conformations and unique combinations of chemical shifts for each. The large uncertainties in the statistical analyses of **1** and **2** shown in Table

5 arise from the relatively small differences in predicted shifts among the different conformers. The largest variations in the C and D rings are predicted to occur at C16 and C14. Thus, in this case it is sensible to take the statistical results only as a qualitative indicator of the major conformers rather than as a meaningful population analysis.

NOESY Studies

The solution state conformations of the 17α side chain of **1** and **2** were also investigated by measuring NOE intensities between the vinyl protons and the aliphatic ^{1}H of the C and D ring. The 2D NOESY of **1** and **2** reveal a similar pattern of NOE cross peaks and intensities between H20 and H21 with the aliphatic protons 12α, 12β, H14, 15α, 16α, and 16β (Figure 5). Selective 1D NOESY experiments of H20 and H21 allow a more detailed inspection of the NOE intensities (Figures 1(c) and 2(c), (d)). Table 6 and 7 summarize and compare the intensities of the observed NOE signals with expected NOE's based on H-H distances in all predicted low energy conformers of **1** and **2**.

The NOE data for **1** and **2** suggest a similarly preferred orientation of the 17α vinyl side chain. The absence of an observable NOE between H21 and 12α rules out conformers, **1c**, **2a**, **2b**, **2c**, **2g**, and **2h**, as contributing conformers, precluding most of the minima observed in the shallow energy surface range of 85° to 165° for dihedral C21-C20-C17-C13 . The observable NOE's between H21 and H14, 15α, and 16α are consistent with **1b** and **2e**. The presence of the extended conformers, **1a**, **2d**, and **2f** are evident from the weak enhancements of 15α and 16α upon irradiation of H20.

Conclusions

The NOE data of **1** and **2** and the statistical analysis of ^{13}C chemical shifts are both

consistent with a preferred orientation of the 17α vinyl side chain. The findings from the multiple independent variable linear regression analyses of the ^{13}C data of **1** and **2**, that conformers **1b** and **2e** are the major conformers, are compatible with the identity of the major conformers favored by NOE data. Conformer **1b** has the vinyl group turned under the D-ring, with the C-21 hydrogen projecting toward C15, and with the C-21 phenyl only slightly twisted out of the plane of the double bond. Conformer **2e** has the double bond disposed in a similar fashion, but has a greater torsion between the double bond and phenyl ring, that allows the ortho substituent to avoid A-strain and to project out from under the D-ring.

The statistical method and the NOE data do not agree on the identity of the minor conformers. For **1**, the regression analysis predicts a 12% population of the extended conformer **1a** that is consistent with the NOE data. However, the minor populations of **1c** and **2c** that appear in the statistical analyses are inconsistent with NOE data that instead favor **2d** and **2f** as minor conformers. The disagreements can be attributed to the limitation of the regression analysis due to the small ^{13}C shift differences in the C and D ring among most of the MM3 predicted conformers. However, the ability of the regression analysis, based on predicted ^{13}C shifts, to identify the same major conformer as identified by NOE data demonstrates that this approach to interpretation of chemical shift data is a useful complement to more common methods of conformational analysis.

This study reveals that the 17α substituents of **1** and **2** have a similar preferred orientation in reference to the steroidal skeleton. This similarity in solution conformations of **1** and **2** suggests that there are no inherent restrictions with respect to occupying a

similar receptor volume other than positional placement of the substituent. Other influences such as electronic effects may also play roles in the differing biological responses and RBA values of **1** and **2**. It is interesting to note the apparent absence of a similar range of conformational structures for the 20E-isomers **1** and **2** compared to the 20Z-isomers previously examined,[3] despite the predictions of favorable energies for other conformers in MM3 calculations. However, with only minor energy differences between conformers, this could be a case where the solution conformational preference could be overridden by interactions with the receptor.

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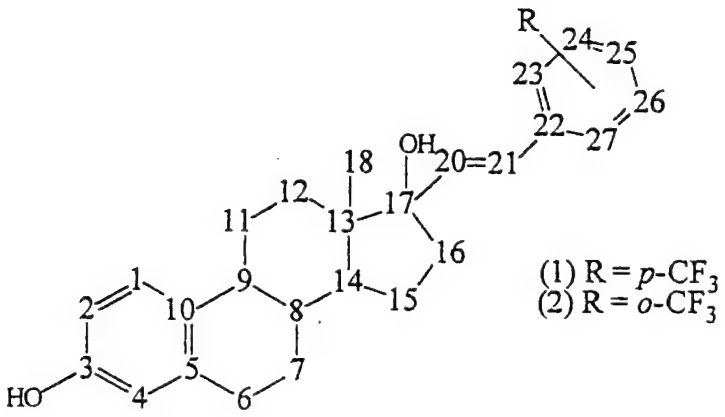


(1) R = *p*-CF_3
(2) R = *o*-CF_3

Figure Captions

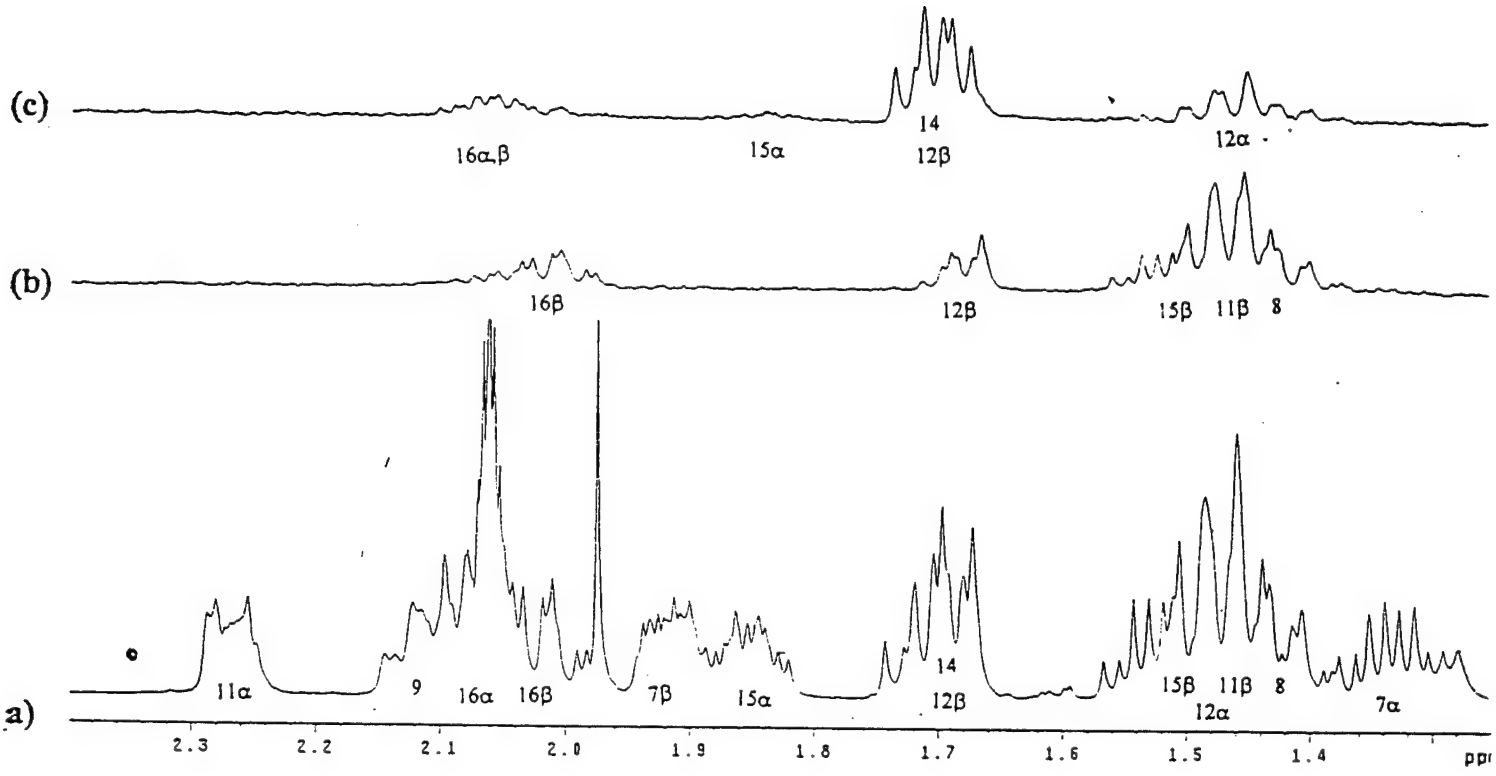
Figure 1. (a) Low frequency spectral region of the 500 MHz ^{1}H NMR spectra of **1** in acetone-d_6. Equivalent spectral regions of the 500 MHz 1D NOESY spectra (500 ms mixing time) of **1** obtained by selective irradiation of the C18 methyl (b), and H20/H21 (c) using a Gaussian pulse. Spectra (b) and (c) are 4x the vertical scale of (a). Overlap of H20 and H21 inhibited selective irradiation of each proton.

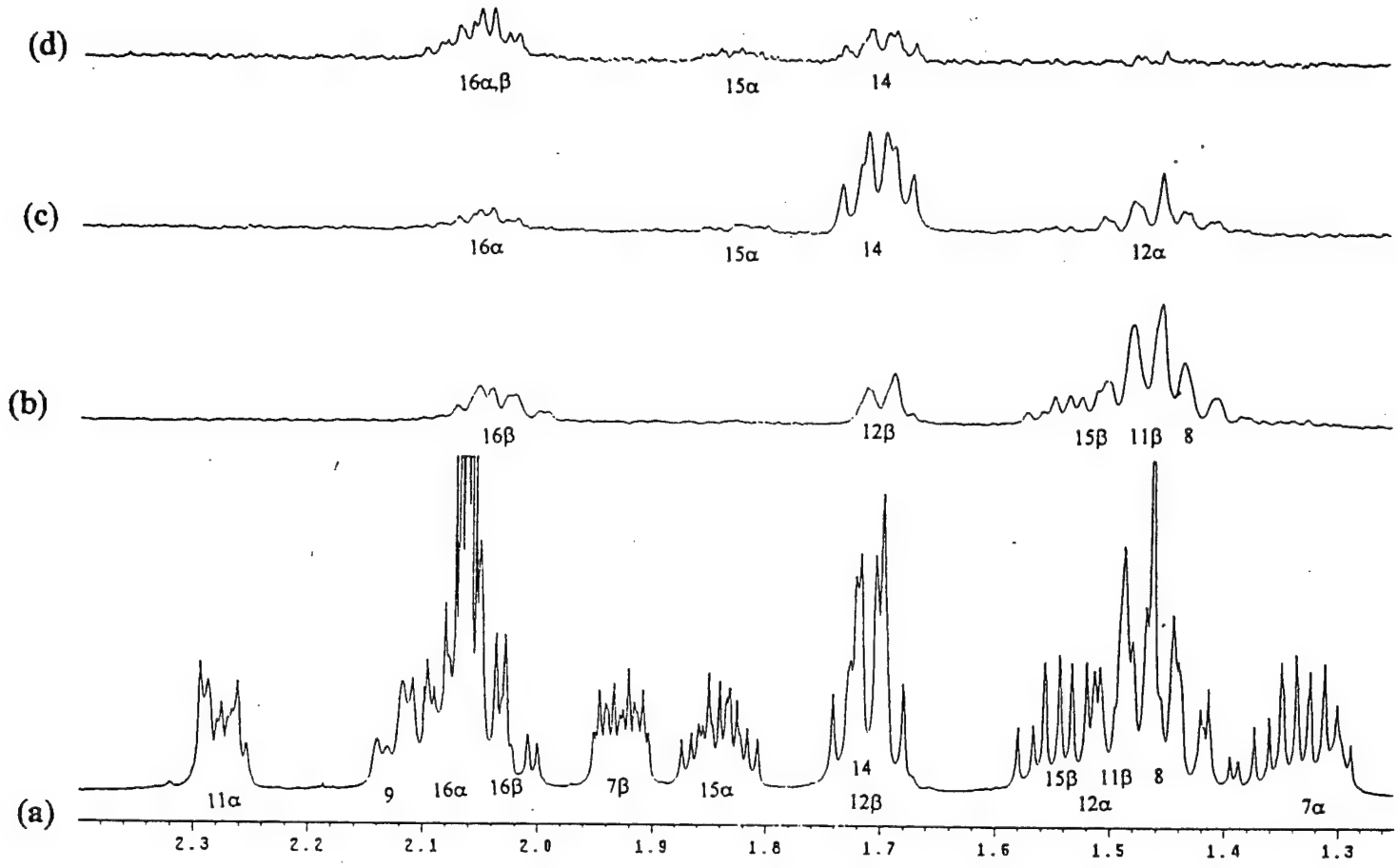
Figure 2. (a) Low frequency spectral region of the 500 MHz ^{1}H NMR spectra of **2** in acetone-d_6. Equivalent spectral regions of the 500 MHz 1D NOESY spectra (500 ms mixing time) of **2** obtained by selective irradiation of the C18 methyl (b), H20 (c), and H21 (d) using a Gaussian pulse. Spectra (b), (c), and (d) are 4x the vertical scale of (a).

Figure 3. MM3-predicted geometries for the most stable conformers of **1**.

Figure 4. MM3-predicted geometries for the most stable conformers of **2**.

Figure 5. Spectral regions of the 500 MHz 2D NOESY spectrum of (a) **1** and (b) **2** obtained with a mixing time of 500 ms. The NOE connectivities are indicated.


(c)
16α,β
15α
14
12β
12α
(b)
16β
12β
15β 11β 8
a)
11α
9
16α 16β
7β
15α
14
12β
15β 11β 8
12α
7α
2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4
ppr


(d)
16α,β
15α
14
(c)
16α
15α
14
12α
(b)
16β
12β
15β
11β
8
(a)
11α
9
16α
16β
7β
15α
14
12β
15β
11β
8
12α
7α
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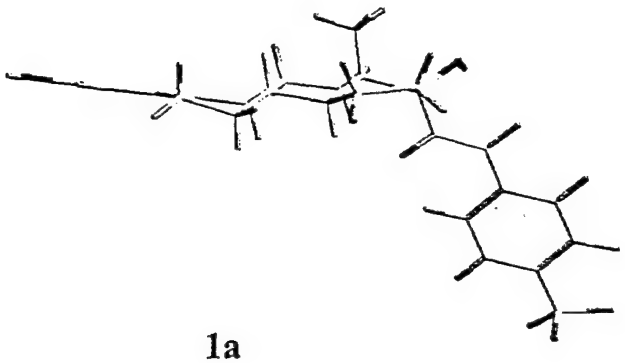
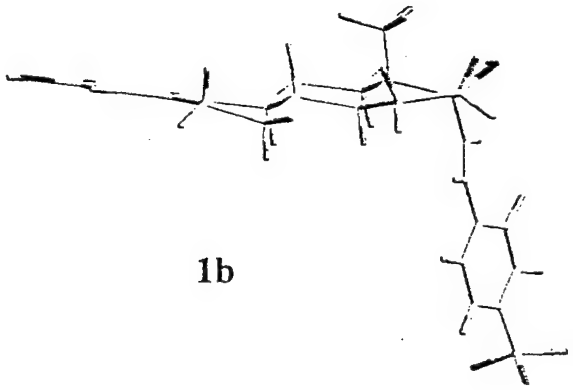
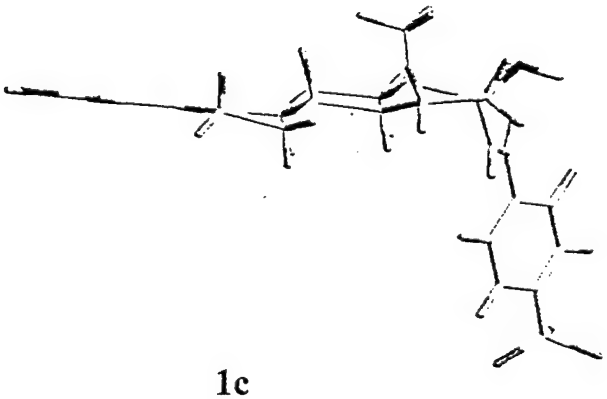
1.8
1.7
1.6
1.5
1.4
1.3



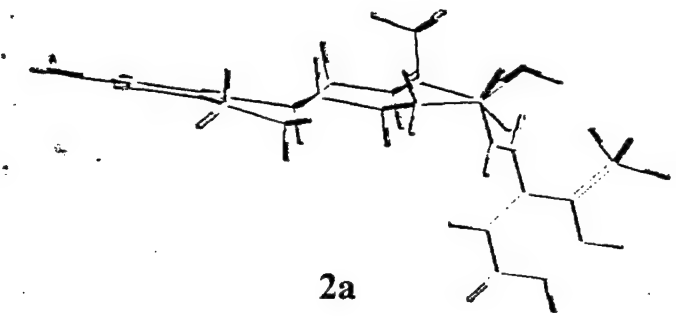
1a



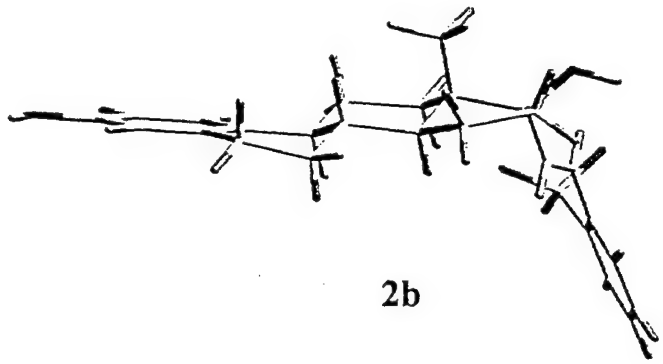
1b



1c



2a



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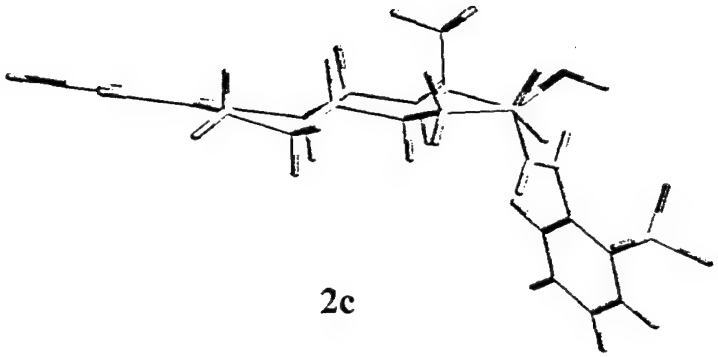

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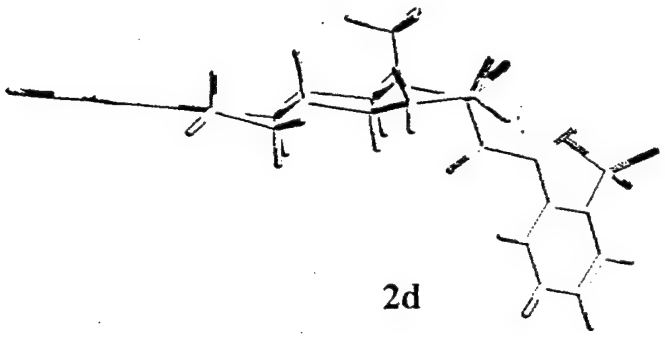
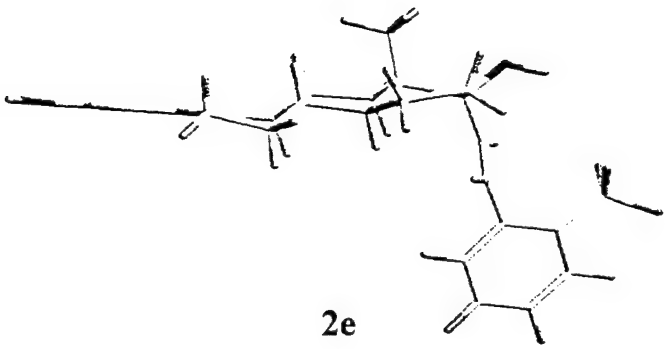
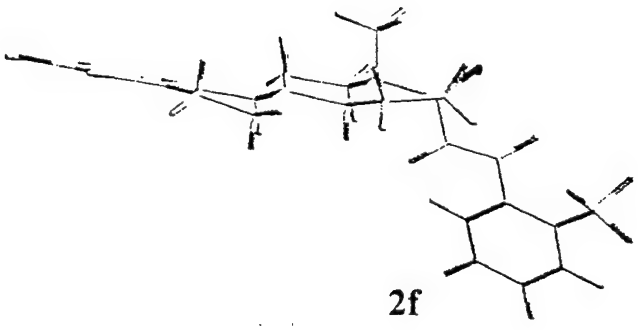


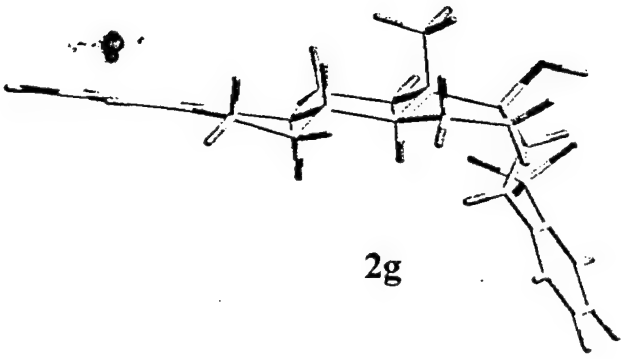
2d



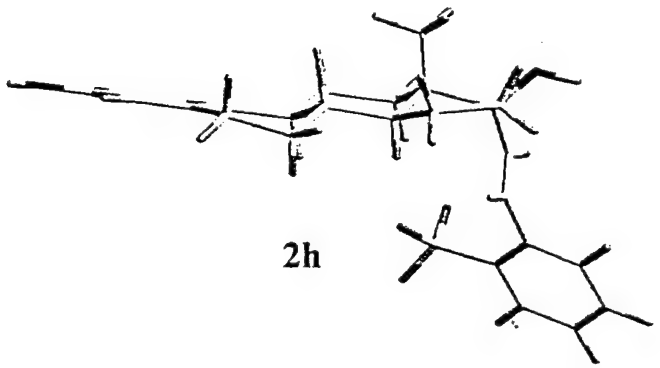
2e



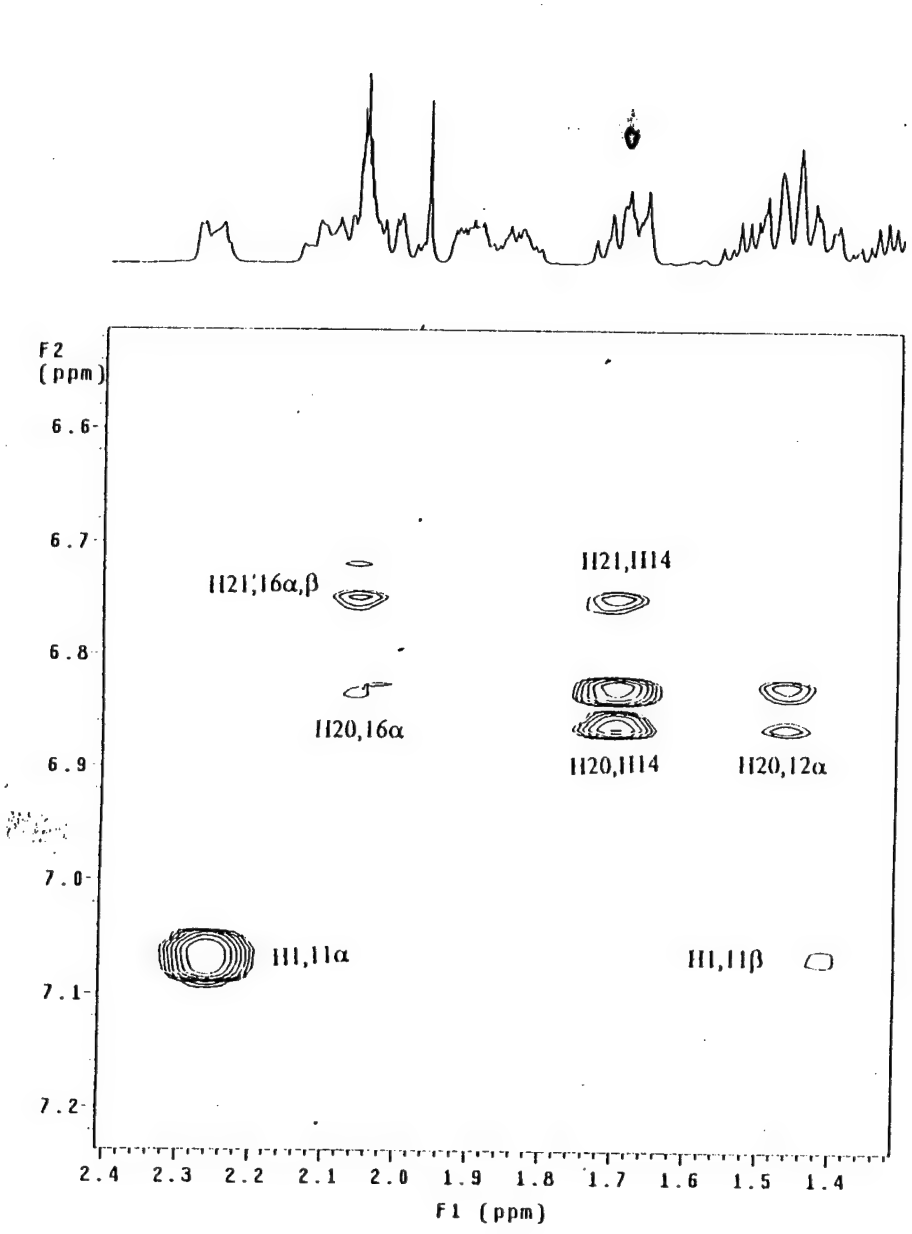
2f



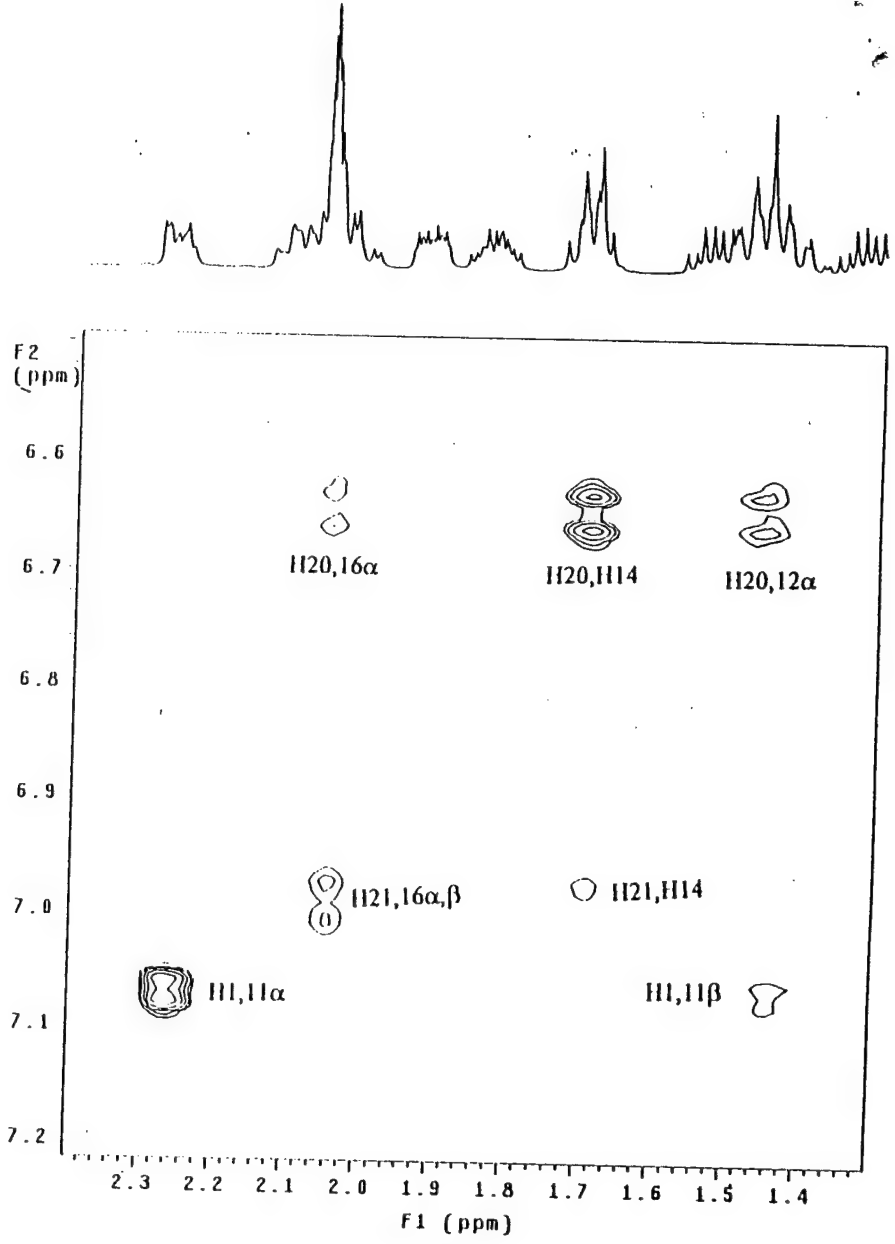
2g



2h


F2
(ppm)
6.6
6.7
6.8
6.9
7.0
7.1
7.2
H21,16α,β
H21,H14
H20,16α
H20,H14
H20,12α
H1,11α
H1,11β
2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4
F1 (ppm)

(a)


F2
(ppm)
6.6
6.7
6.8
6.9
7.0
7.1
7.2
H20,16α
H20,H14
H20,12α
H21,16α,β
H21,H14
H1,11α
H1,11β
2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4
F1 (ppm)

(b)

Table 1. ^{1}H and ^{13}C Chemical Shifts for **1** and **2**

^{1}H	1	2	^{13}C	1	2
1	7.09	7.09	1	126.4	126.4
2	6.58	6.59	2	112.9	112.9
4	6.52	6.54	3	155.3	155.2
6α	2.75	2.78	4	115.3	115.3
6β	2.80	2.81	5	137.7	137.5
7α	1.32	1.34	6	30.0	29.9
7β	1.92	1.92	7	27.7	27.7
8	1.43	1.54	8	40.1	40.0
9	2.10	2.10	9	44.0	44.0
11α	2.26	2.28	10	131.3	131.3
11β	1.46	1.43	11	26.7	26.6
12α	1.42	1.50	12	32.9	32.8
12β	1.68	1.69	13	47.8	47.8
14	1.70	1.71	14	49.5	49.4
15α	1.86	1.84	15	23.5	23.5
15β	1,52	1.50	16	37.0	36.9
16α	2.04	2.04	17	83.6	83.7
16β	2.06	2.06	18	14.2	14.1
CH_3	1.02	1.01	20	140.0	141.8
20	6.74	6.65	21	125.3	122.9
21	6.85	7.0	22	142.1	137.8
23	7.69	N/A	23	127.0	127.6
24	7.64	7.70	24	125.6	125.7
25	N/A	7.61	25	128.9	132.6
26	7.64	7.44	26	125.6	127.2
27	7.69	7.82	27	128.2	128.0
N/A	N/A	N/A	CF_3	125.4	125.7

Table 2. Relative Energies and Key Dihedrals of Predicted Conformers of **1** and **2** Using MM3

Conformers	C13-C17-C20-C21	C20-21-22-23	Relative Energies (kcal/mol)
1a	161	-169	0
1b	-96	18	0.30
1c	89	158	0.32
2a	87	-145	0
2b	95	151	0.06
2c	89	-56	0.92
2d	149	144	1.25
2e	-99	55	1.26
2f	162	-148	1.33
2g	-65	-49	1.53
2h	-95	-68	1.59

Table 3. Experimental and Predicted ^{13}C Chemical Shifts (ppm) of Predicted Conformers of **1** Using B3LYP/3-21G(X,6-31+G*)//MM3 Calculations

Carbon	1a	1b	1c	expt
C1	127.6	127.2	127.3	126.4
C2	113.2	113.1	113.1	112.9
C3	153.3	153.1	153.0	155.3
C4	116.1	115.8	115.7	115.3
C5	136.4	136.0	135.9	137.7
C6	31.2	30.8	30.7	30.0
C7	28.2	28.3	28.3	27.7
C8	40.3	39.8	39.5	40.1
C9	44.2	43.9	43.9	44.0
C10	131.6	131.5	131.8	131.3
C11	28.3	28.1	28.2	26.7
C12	31.4	31.8	32.4	32.9
C13	46.5	48.1	48.1	47.8
C14	50.2	48.0	47.9	49.5
C15	25.7	26.2	26.4	23.5
C16	45.9	36.8	39.2	37.0
C17	83.0	84.9	84.1	83.6
C18	15.2	16.6	15.5	14.2
C20	149.2	144.9	143.4	140.0
C21	133.9	131.6	131.3	125.3
C22	137.9	138.6	137.6	142.1
C23	121.6	122.4	122.0	127.0
C24	127.5	127.6	127.5	125.6
C25	132.2	131.7	131.8	128.9
C26	128.0	127.8	127.8	125.6
C27	129.3	128.5	129.2	128.2
C28	130.8	130.9	130.8	125.4

Table 4. Experimental and Predicted ^{13}C Chemical Shifts (ppm) of Predicted Conformers of **2** Using B3LYP/3-21G(X,6-31+G*)//MM3 Calculations

Carbon	2a	2b	2c	2d	2e	2f	2g	2h	expt
C1	127.4	127.6	127.3	127.5	127.5	127.4	127.6	127.6	126.4
C2	113.1	113.1	113.0	113.1	113.1	113.1	113.1	113.0	112.9
C3	153.1	152.9	153.0	153.0	153.0	153.1	153.1	152.9	155.2
C4	115.8	115.5	115.8	115.8	115.7	115.9	115.8	115.7	115.3
C5	136.2	135.8	136.1	136.1	136.1	136.3	136.2	136.2	137.5
C6	31.1	30.8	30.7	31.1	31.1	30.9	31.1	31.1	29.9
C7	28.3	28.4	28.1	28.3	28.3	28.2	28.4	28.3	27.7
C8	39.9	39.7	40.1	39.9	39.5	40.1	40.3	40.0	40.0
C9	44.3	44.4	44.2	44.3	44.3	44.3	44.5	44.2	44.0
C10	131.6	132.1	131.6	131.6	132.0	131.5	131.7	132.1	131.3
C11	28.3	28.5	28.5	28.2	28.3	28.2	28.4	28.4	26.6
C12	33.0	33.8	33.1	31.9	32.2	31.9	29.4	30.5	32.8
C13	48.1	48.6	48.0	47.7	47.2	47.2	48.6	47.6	47.8
C14	51.5	51.1	50.9	49.6	48.3	49.7	50.8	47.6	49.4
C15	26.0	26.5	26.0	25.8	26.4	25.6	26.8	26.1	23.5
C16	39.6	42.4	39.2	39.6	38.9	41.6	39.7	37.6	36.9
C17	83.6	83.9	84.6	84.0	83.6	84.0	81.9	85.5	83.7
C18	16.3	15.0	16.1	16.3	15.2	16.3	18.3	16.9	14.1
C20	146.2	146.7	151.2	146.3	151.1	147.5	149.6	151.2	141.8
C21	130.7	133.3	130.1	129.9	225.7	132.5	128.7	131.7	122.9
C22	137.2	137.5	140.8	138.6	140.4	138.7	140.7	140.6	137.8
C23	126.8	126.4	128.1	127.3	128.4	126.6	128.7	129.0	127.6
C24	131.9	131.9	130.7	132.1	130.9	131.9	130.9	131.0	125.7
C25	130.6	130.6	130.9	130.9	131.0	130.7	130.9	130.8	132.6
C26	127.8	127.6	129.5	127.7	129.5	127.7	129.3	129.0	127.2
C27	130.5	130.1	131.4	130.1	131.2	130.0	131.0	130.5	128.0
C28	126.8	126.5	126.0	126.3	126.2	126.6	126.3	126.1	125.7

Table 5. Summary of the Multiple Independent Variable Regression Analysis[a] of the Calculated ^{13}C Shifts of Predicted Conformers of **1** and **2**

Conformer	Estimate (%)	Standard Error (%)
1a	13	29
1b	72	32
1c	15	28
2a	0	14
2b	0	13
2c	33	18
2d	0	18
2e	65	33
2f	0	30
2g	0	4
2h	2	22

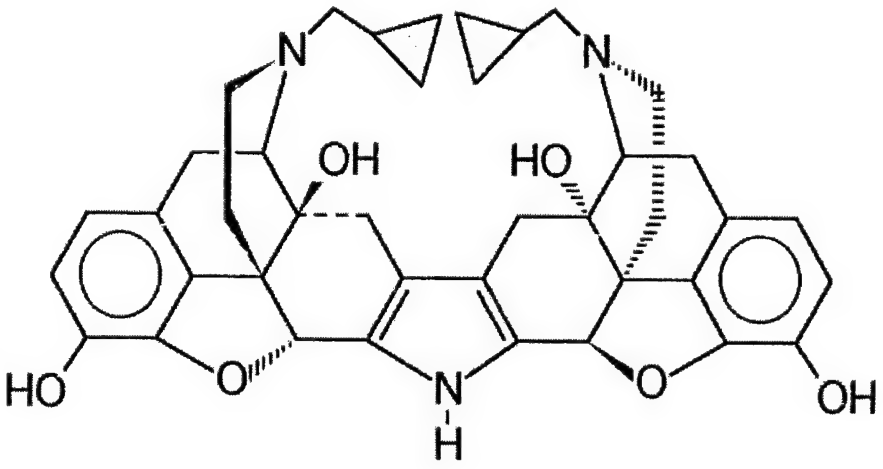
[a] Constraints: Each conformer is greater than or equal to 0 %. Each of the conformer sets **1a-1c** and **2a-2h** total to 100 %.

Table 6. Summary and Comparison of Observed NOE Enhancements with Expected NOE Intensities[a] for Predicted Conformers of **1**

Irradiated	Enhanced	1a	1b	1c	Expt
H20	12α	s	s	w	**s**
H20	H14	s	s	s	**s**
H20	15α	w	n	w	**w**
H20	16α,β	w	n	w	**w**
H21	12α	n	n	s	**n**
H21	H14,12β	n	s	w	**w**
H21	15α	n	w	n	**w**
H21	16α,β	n	s	n	**s**

a. Expectations of strong (s), weak (w), and no (n) NOE enhancements correspond to H-H distances of 0 - 2.99; 3.0 - 4.99; and > 5 Å.

The Philip S. Portoghese Symposium in Medicinal Chemistry



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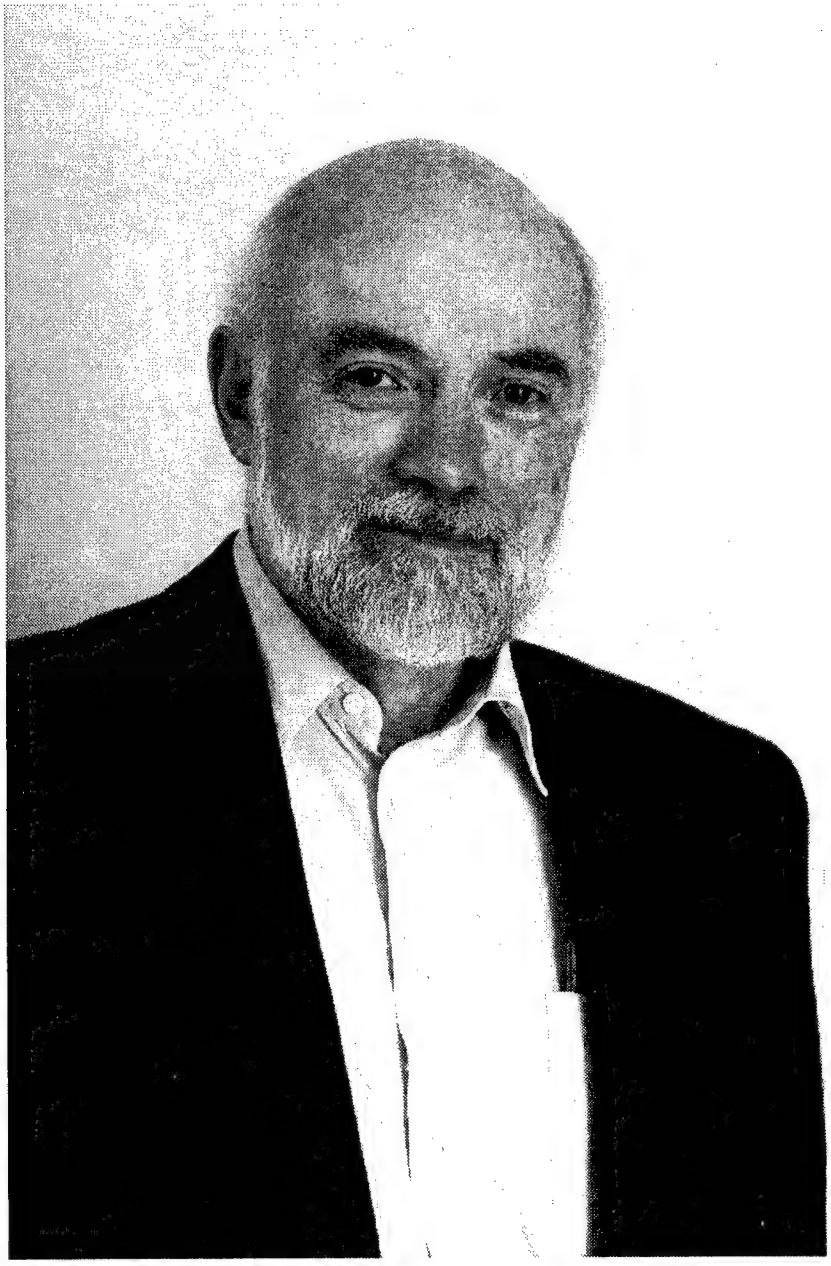
University of Minnesota



Philip S. Portoghese, Ph.D.

Philip S. Portoghese, Ph.D., is a University Distinguished Professor of Medicinal Chemistry at the University of Minnesota. A graduate of the University of Wisconsin Medicinal Chemistry department, he has served on the faculty at Minnesota since 1961. Dr. Portoghese is a member of the editorial or editorial advisory boards of many journals and scientific organizations, and has been the Editor-in-Chief of the *Journal of Medicinal Chemistry* since 1972. He has received honorary doctorate degrees from the University of Catania, Italy and the Royal Danish School of Pharmacy. He is the recipient of many awards including the A.Ph.A. Research Achievement Award (1980), the Volwiler Award (1984), the ACS Medicinal Chemistry Award (1990), the AAPS Research Achievement Award in Medicinal Chemistry (1990), the Nathan Eddy Award (1991), the ACS Edward Smissman Award (1991), the Rho Chi Pharmacy Honor Society Award (1999), the Italian Chemical Society Oak & Tulip Award (1999), and the ACS Alfred Burger Award (2000). He is a fellow of the Academy of Pharmaceutical Sciences (1974), AAAS (1986), AAPS (1986) and College on Problems of Drug Dependence (1990).

Prof. Portoghese has presented numerous lectures at national and international conferences, universities and industry, has authored over 315 publications and has trained approximately 95 students and postdoctoral research associates. His research interests are in the area of drug design with specific contributions to the area of opioid chemistry. The impact of his work on the field of drug design and receptor-ligand interactions is exemplified by him being listed as one of the most cited authors in the area of xenobiotics for the period 1981-1992.

On the occasion of his 70th birthday, we would like to celebrate Phil's outstanding contributions not only as a preeminent scholar in medicinal chemistry, but also in his teaching and mentoring of scientists, as well as his outstanding service as Editor of the *Journal of Medicinal Chemistry*. He has uniquely contributed to the quality and reputation of the Department of Medicinal Chemistry, the College of Pharmacy, and the University of Minnesota.

PROGRAM

August 23, 2001
2-530 Moos Tower

8:30 **Registration**

9:00 **Welcome and Introduction**

Yusuf Abul-Hajj, Ph.D., Professor and Head
Department of Medicinal Chemistry, University of Minnesota

Marilyn Speedie, Ph.D., Dean
College of Pharmacy, University of Minnesota

MODERATOR: Yusuf Abul-Hajj, Ph.D., *University of Minnesota*

9:15 ***"SPECIFIC $GABA_A$ RECEPTOR LIGANDS: FROM MUSHROOM CONSTITUENT THROUGH CLINICALLY ACTIVE DRUG TO RATIONAL DRUG DESIGN"***
Povl Krosgaard-Larsen, Ph.D., *Royal Danish School of Pharmacy*

9:55 ***"DOPAMINE RECEPTORS IN THE CENTRAL NERVOUS SYSTEM: TARGETS FOR MEDICINAL CHEMISTS PAST, PRESENT AND FUTURE"***
John L. Neumeyer, Ph.D., *Harvard University*

10:35-11:00 **Break**

11:00 KEYNOTE ADDRESS
Ralph Hirschmann, Ph.D., *University of Pennsylvania*

12:00-1:30 Lunch Break

MODERATOR: Rick Wagner, Ph.D., *University of Minnesota*

1:30 ***"DESIGN AND SYNTHESIS OF PEPTIDASE INHIBITORS. WHAT CHALLENGES REMAIN?"***
Daniel H. Rich, Ph.D., *University of Wisconsin*

2:10 ***"DESIGN, SYNTHESIS AND EVALUATION OF NOVEL STEROIDAL ANTIESTROGENS FOR THE TREATMENT OF HORMONE RESPONSIVE BREAST CANCER"***
Robert N. Hanson, Ph.D., *Northeastern University*

2:50-3:20 Break

3:20 ***"G-QUADRUPLEXES AND ASSOCIATED GENE TARGETS FOR DRUG DESIGN"***
Laurence H. Hurley, Ph.D., *University of Arizona*

4:00 ***"BENZODIAZEPINE CCK-A RECEPTOR AGONISTS"***
Elizabeth E. Sugg, Ph.D., *GlaxoSmithKline Company*

4:40 ***"2(3H)-BENZOTHIAZOLONES, AN INEXHAUSTIBLE SOURCE OF INSPIRATION FOR AN ACADEMIC MEDICINAL CHEMIST. APPLICATION TO THE DESIGN OF MIXED AFFINITY LIGANDS FOR 5-HT SUB-CLASSES"***
Jacques Poupaert, Ph.D., *University of Louvan, Belgium*

6:30 **Reception** – Cash Bar
McNamara Alumni Center, A.I. Johnson Great Room

7:30 **Dinner** – Pre-registered guests only
McNamara Alumni Center, A.I. Johnson Great Room

August 24, 2001
2-530 Moos Tower

MODERATOR: David Ferguson, Ph.D., *University of Minnesota*

8:30 *"OPIOID RECEPTORS: STRUCTURAL INSIGHTS INTO RECEPTOR FUNCTION AND LIGAND INTERACTION FROM MOLECULAR MODELING"*
M. Germana Paterlini, Ph.D., *University of Minnesota*

9:00 *"EVOLUTION OF THE 3,4-DIMETHYL-4-PHENYLPIPERIDINE OPIOID ANTAGONISTS: FROM DISCOVERY AND PHARMACOLOGICAL CHARACTERIZATION TO THERAPEUTIC DEVELOPMENT"*
Dennis M. Zimmerman, Ph.D., *Lilly Research Laboratory*

9:40 *"DEVELOPMENT OF SELECTIVE OPIOID ANTAGONISTS"*
F. Ivy Carroll, Ph.D., *Research Triangle Institute*

10:20-10:50 Break

10:50 *"EXPLORING THE CHEMISTRY OF PAIN AND ADDICTION WITH A NEW PARADIGM."*
Victor J. Hruby, Ph.D., *University of Arizona*

11:30 *"OPIOID PEPTIDE ANALOGUES AND PEPTIDOMIMETICS AS PHARMACOLOGICAL TOOLS AND POTENTIAL DRUGS"*
Peter W. Schiller, Ph.D., *Research Institute of Montreal*

12:10-1:30 Lunch Break

MODERATOR: Herbert Nagasawa, Ph.D., *University of Minnesota*

1:30 *"OPIOID RESEARCH TOOLS AND DRUGS FOR THE NEW MILLENNIUM"*
Kenner C. Rice, Ph.D., *National Institutes of Health*

2:10 *"DESIGN AND SYNTHESIS OF NOVEL PEPTIDE-BASED AFFINITY LABELS FOR OPIOID RECEPTORS"*
Jane V. Aldrich, Ph.D., *University of Maryland*

2:50-3:20 **Break**

3:20 *"DEVELOPMENT OF POTENT AND HIGHLY SELECTIVE SMALL MOLECULE INHIBITORS OF VLA4"*
Francine S. Grant, Ph.D., *Elan Pharmaceuticals*

4:00 *"SELECTIVE MECHANISM-BASED INHIBITION OF THE QUINONE-DEPENDENT AMINE OXIDASES"*
Lawrence M. Sayre, Ph.D., *Case Western Reserve University*

4:40 **Symposium Summation**
Yusuf Abul-Hajj, Ph.D.

4:45 "WORDS OF WISDOM"
Philip S. Portoghese, Ph.D.

Graduate Students and Research Associates

Anthony Abatjolgou
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